



Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
1 617-252-7500

May 26, 2006

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20852

Re: Comments of Genzyme Corporation
Docket No.: 2006P-0186

The following constitutes the initial comments of Genzyme Corporation, manufacturer of Renagel[®] (sevelamer hydrochloride) tablets ("Renagel") on the Citizen Petition dated May 3, 2006, filed by Charles R. Nolan, M.D. (the "Citizen Petition"). Renagel is indicated for the control of serum phosphorus in patients with chronic kidney disease on hemodialysis. In his petition, Dr. Nolan requests that FDA withdraw approval of Renagel tablets, 400 and 800 mg or, alternatively, require that the labeling for Renagel tablets contain a "black box" warning regarding an alleged risk of intestinal obstruction and perforation. For the reasons stated below, the petition should be denied.

The Citizen Petition appears to be based almost entirely on data compiled by the petitioner from the FDA AERS (Adverse Event Reporting System) database, which the petitioner characterizes as showing a "disturbing number of reports of intestinal obstructions and perforations associated with the use of Renagel in dialysis patients." To support these conclusions, the petitioner asserts that (1) since 1999, AERS data indicate that 80 cases of gastrointestinal obstruction and 79 cases of gastrointestinal perforation (some fatal) have been reported; (2) during the period from first quarter 2004 through third quarter 2005, Renagel was associated with 133 reported events of intestinal obstruction and perforation (65 intestinal obstruction, 68 intestinal perforation), a number of which are alleged to have had a fatal outcome, with other products reporting fewer events (Fosrenol^{®1} with three intestinal obstructions; PhosLo^{®2} with no such GI events); while the overall number of adverse events over that period showed 1633 for Renagel, 354 for Fosrenol and 21 for PhosLo.³

As set forth below, Dr. Nolan's petition mischaracterizes the results obtained from the AERS database and ignores significant patterns in the safety data relating to Renagel, including a concentration of adverse event reports in the Japanese population. The Citizen Petition's suggestions regarding the Renagel label are therefore unfounded. Renagel is a safe and effective product that has been used by over 750,000 patients in the United States and 50 countries throughout the world since 1998. In several published clinical studies, Renagel has been found to be safe and as effective as

¹ Fosrenol is a registered trademark of Shire.

² PhosLo is a registered trademark of Nabi Biopharmaceuticals. Dr. Nolan has indicated that he is a paid consultant to Nabi.

³ Importantly, the overall number of adverse events presented in the Citizen Petition for Renagel are from worldwide exposure, whereas the overall number of adverse events for Fosrenol and PhosLo are only from U.S. exposure.

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other widely marketed phosphorus binder products, including the calcium-based products referred to in the Citizen Petition. Moreover, unlike calcium-based binders, Renagel is not absorbed, and therefore does not increase calcium load or risks associated with excess calcium.

I. The Citizen Petition seriously mischaracterizes the AERS safety data for Renagel.

The public AERS database, which is the sole source relied upon by Dr. Nolan for his analysis, is the FDA's worldwide adverse event reporting system, a computerized information database that is available to the public and designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The AERS database is considered the best available system for collecting post-marketing adverse event reports. However, as explained by FDA in a recent letter to Congressman Souder involving a review of the safety of mifepristone, or RU-486, the AERS database "cannot be used to calculate actual incidences of adverse events or estimates of risk for a product . . ." ⁴ Moreover, FDA further explained that,

AERS reports alone would not commonly provide a sufficient basis for either FDA or sponsor action, since AERS reporting generally does not support causality assessments and does not allow for accurate assessment of the frequency of an event in relation to drug use. ⁵

As FDA notes, in addition to the underreporting inherent in a voluntary process, the AERS database is influenced by other factors, such as duration of marketing, market share, sales force size and sophistication, publicity about an adverse reaction, and regulatory actions. ⁶ Of particular import here, the AERS database, as FDA also recognizes, "often contains multiple reports of the same incident" and that "in some instances, the same event in the same patient can be reported more than once because of duplicate reporting (e.g., a physician sends the report directly to FDA as well as to the company, which in turn sends the report to FDA)." ⁷

Other instances in which Genzyme believes the same event may be reported multiple times include: reports identifying multiple drugs; reports where multiple sponsors submit the same case; reports where follow-up reports are not linked to initial reports; reports where corrections are not made despite submission of a change to the case; as well as others. In addition to duplicative information, the AERS database limits the ability to identify the country of origin of reports, thereby restricting analysis of reports in the context of particular regional or geographic considerations. Also, based on all these factors, cross-product comparisons based on AERS data are unreliable.

⁴ Ltr, David W. Boyer, Assistant Commissioner for Legislation, FDA, to Rep. Mark E. Souder, Subcommittee on Criminal Justice, Drug Policy and Human Resources, House Committee on Government Reform; May 2, 2006, p. 1. See Attachment 1.

⁵ Ltr., p. 4.

⁶ Ltr., p. 1.

⁷ Ltr., pp. 1-2.

Genzyme has reviewed Dr. Nolan's use of the AERS numbers, and has found no indication that Dr. Nolan recognized the various limitations of the AERS database, or attempted to account for those limitations in his analysis. More important, Dr. Nolan fails to identify that the increases in reported gastrointestinal events are limited to a particular country, Japan, and can be explained by multiple factors unique to the population in Japan in the period following introduction of the product to the market in 2003.

On the basis of its own Global Safety Database, which Genzyme has reconciled to the AERS database, Genzyme has identified the degree to which Dr. Nolan's analysis reflects duplicative reports regarding ileus, gastrointestinal obstruction and gastrointestinal perforation for patients on Renagel worldwide. Figure 1 and Table 1 reflect the discrepancies between the reported gastrointestinal adverse events presented by Dr. Nolan from the AERS database compared to the Genzyme Global Safety Database. As seen in Figure 1 and Table 1, analysis of data from the Genzyme Global Safety Database reveals significantly lower numbers of these events than those presented in the Citizen Petition. As further reflected in Figure 1 and Table 1, during the 7-year period from 1999 to 2005, 88 percent of the reports of ileus, intestinal obstruction and intestinal perforation were reported from Japan and correspond to the Japanese launch of sevelamer hydrochloride in June 2003.

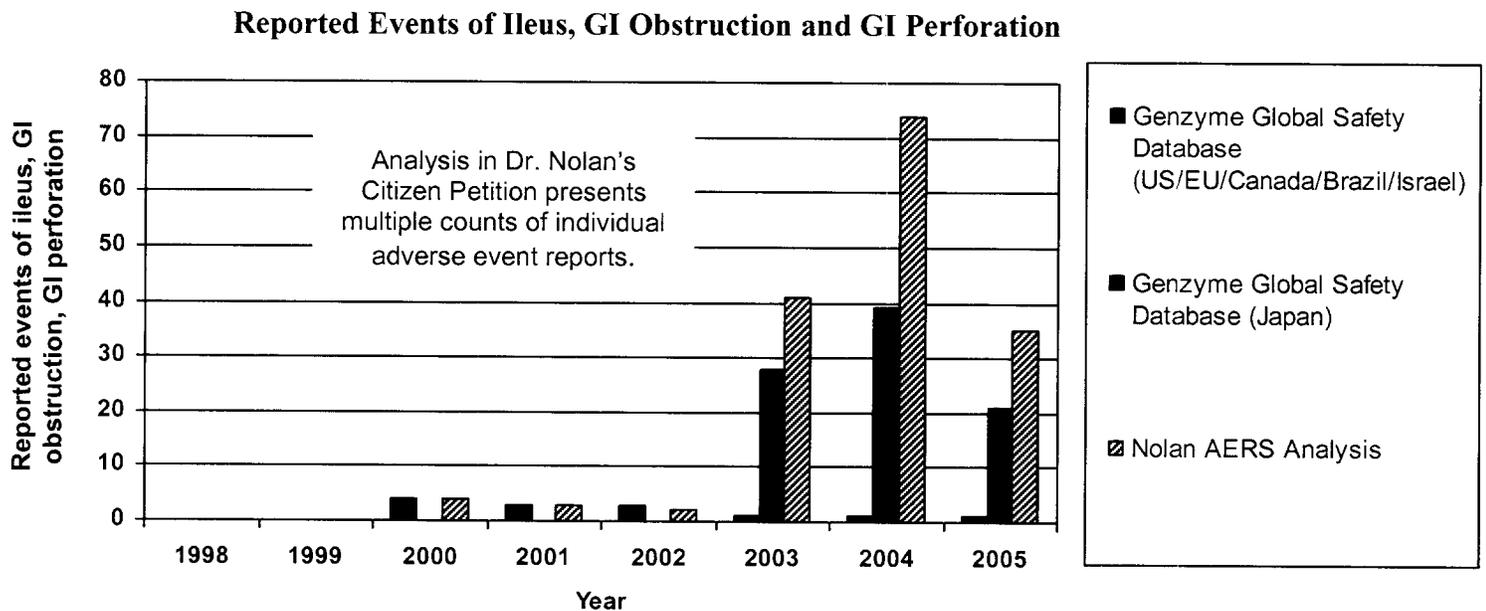


Figure 1

Source: Dr. Nolan Citizen Petition and Genzyme Global Safety Database

Reported events of ileus, gastrointestinal obstruction, gastrointestinal perforation in Genzyme Global Safety Database compared to Dr. Nolan’s analysis from the AERS Database

Time Period	Genzyme Renagel 400/800 mg tablet formulation (US, Europe, Canada, Brazil, Israel) <i>Estimated cumulative exposure: 750,000 patients</i>			Chugai / Kirin (MAH in Japan) Renagel / Phosblock 250 mg tablet formulation (Approval in Japan: June 2003) <i>Estimated cumulative exposure: 45,000 patients</i>			Dr. Nolan’s AERS Analysis in Citizen Petition*	
	Ileus	Intestinal Obstruction	Intestinal Perforation	Ileus	Intestinal Obstruction	Intestinal Perforation	GI Obstruction	GI Perforation
2005**	0	1	0	5	2	14	15	20
2004	0	1	0	9	10	20	31	43
2003	0	1	0	6	12	10	26	15
2002	0	1	2	Not yet commercialized in Japan			1	1
2001	1	2	0				3	0
2000	0	3	1				4	0
1999	0	0	0				0	0
Totals	1	9	3	20	24	44	80	79

* Dr. Nolan identified events by key search words “ileus”, “obstruction” and “perforation” (ileus not separated in analysis)

** AERS data time period: January 2005 – September 2005

Table 1

In summary, these data clearly show that Dr. Nolan’s analysis of the AERS data for Renagel does not present an accurate assessment of the worldwide frequency of these gastrointestinal events.

II. Data from clinical trials, post-marketing experience and other sources do not support the allegations regarding gastrointestinal adverse events associated with Renagel use.

In global clinical trials with Renagel, there has been no evidence of a safety concern regarding ileus, gastrointestinal obstruction or gastrointestinal perforation. Clinical trials forming the basis for the U.S. approval of Renagel found no safety signal regarding ileus, gastrointestinal obstruction or gastrointestinal perforation. Subsequently, in the one-year “Treat-to-Goal” Study⁸ (100 patients on Renagel, 102 patients on calcium binders) together with the add-on one year “Treat-to-Goal Extension Study,”⁹ two patients experienced serious gastrointestinal events considered possibly related to Renagel by the investigators. However, the patients’ co-morbid conditions or complicated procedures were the primary contributors to the events. The Dialysis Clinical Outcomes Revisited trial or “DCOR” trial treated 1033 patients with Renagel and 1007 patients with calcium binders and

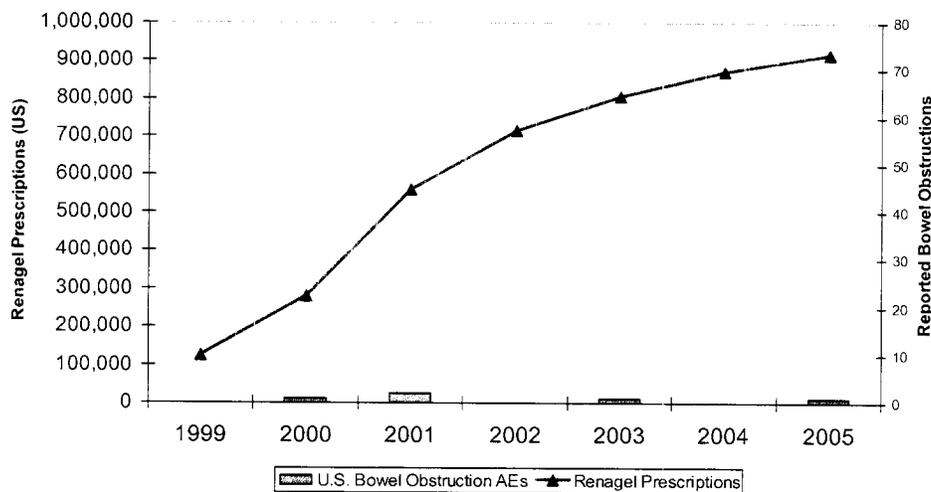
⁸ Chertow, G. M., et al. 2005. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney International*, Vol. 68: 1815-1824. See Attachment 2.

⁹ Asmus, H.G., et al. 2005. Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. *Nephrology Dialysis Transplantation*, Vol. 20: 1653-1661. See Attachment 3.

followed these patients for up to 45 months. No serious related events of ileus, gastrointestinal obstruction or gastrointestinal perforation were reported during this trial.

Since the launch of Renagel in the United States in 1998 (and in much of the remaining world countries since 2000), reports of ileus, gastrointestinal obstruction, and/or gastrointestinal perforation have not increased in frequency despite the consistently increasing number of prescriptions annually. Figure 2 reflects the constant, very low level of obstruction events reported in the United States since 2000 compared to increasing numbers of U.S. total prescriptions. Reports of gastrointestinal obstruction from the United States have been rare, and information received on these cases revealed that patient medical history and/or co-morbidities may have contributed to the events. No reports of either ileus or gastrointestinal perforation were reported in the U. S. during the years in question.

**US Renagel Prescriptions vs
US Reported Bowel Obstructions**

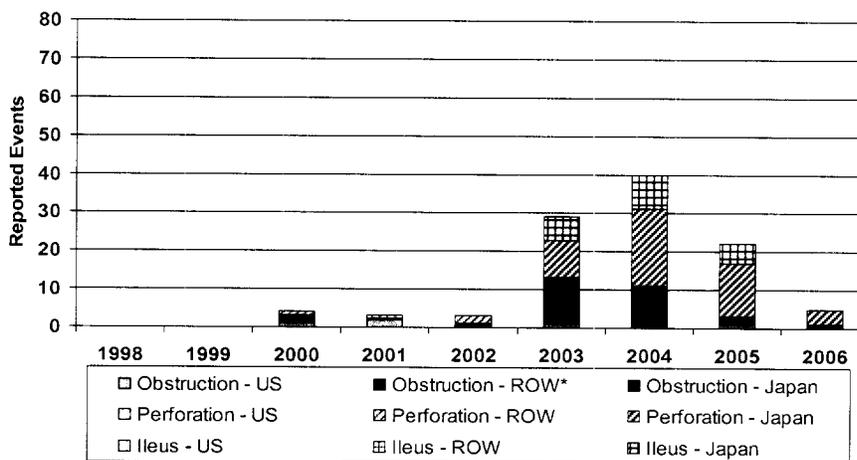


Source: Rx data from IMS NPA and Genzyme Global Safety Database

Figure 2

As noted in Section 1, the great majority of reports of ileus, gastrointestinal obstruction, or gastrointestinal perforation received by Genzyme since the introduction of Renagel in 1998 were reported from Japan and correspond to the Japanese launch of sevelamer hydrochloride in June 2003. Reported events worldwide of ileus, gastrointestinal obstruction or gastrointestinal perforation are presented by region in Figure 3.

Reported Events of Ileus, GI Obstruction and GI Perforation by Region



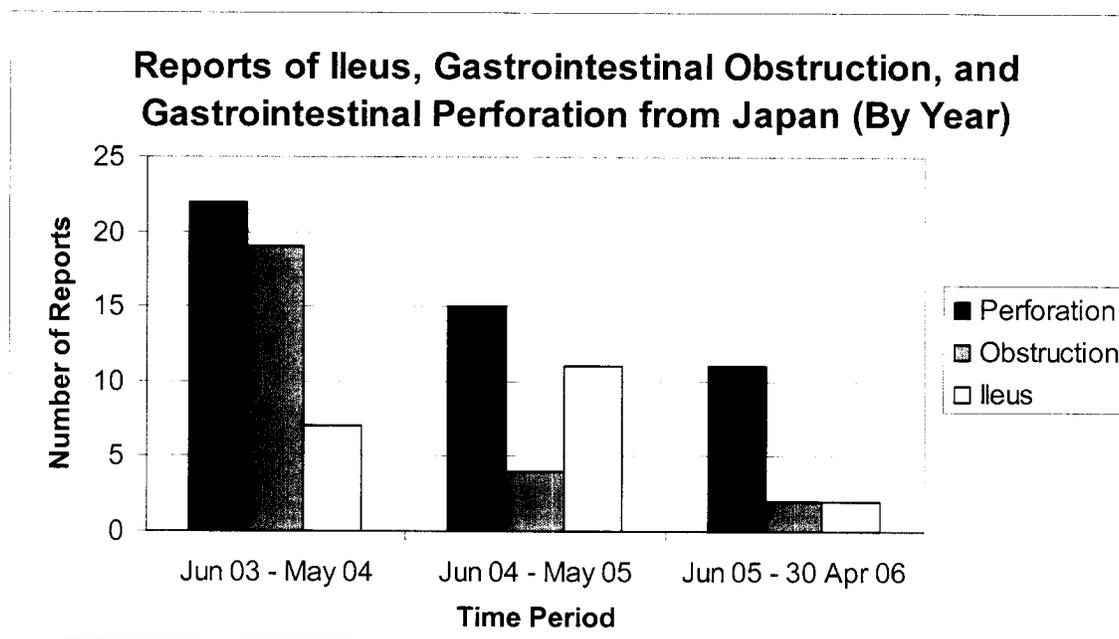
*ROW = Rest of World (EU, Canada, Brazil, Israel)

Source: Genzyme Global Safety Database

Figure 3

In Japan, sevelamer hydrochloride is formulated as a 250 mg tablet and commercialized as Phosblock[®] and Renagel by Genzyme's partners, Kirin and Chugai. The reasons for the substantially higher number of reported GI adverse events in Japan in the period immediately after launch are likely multi-factorial. Varied ethnic and cultural factors including diet and medicinal and healthcare practices are all potential reasons. Additionally, in the six months immediately following the launch of the product in Japan, moreover, regulatory requirements provided that adverse events be actively solicited from healthcare providers, increasing the number of reports received.

Following the introductory period, there has been a continuing documented decrease in the number of reports of intestinal obstruction/intestinal perforation received from Japan, as shown in Figure 4, while use of sevelamer hydrochloride has continued to increase in Japan.



Source: Genzyme Global Safety Database

Figure 4

The Citizen Petition, in presenting Dr. Nolan's interpretation of the AERS safety data for Renagel, states that "a number of intestinal obstructions and perforations had a fatal outcome." However, the number of ileus, intestinal obstruction and intestinal perforation fatalities reported in patients on Renagel is extremely low. Although reports of ileus, gastrointestinal obstruction and gastrointestinal perforation fatalities from Japan are higher, these deaths are not clearly attributed to sevelamer hydrochloride use.

Outside Japan, three deaths in Renagel patients with gastrointestinal obstruction or gastrointestinal perforation have been reported since the 1999 product introduction, notwithstanding that the Renagel patient population, chronic kidney disease patients on hemodialysis, suffers generally from high levels of morbidity and mortality. No deaths were associated with ileus. In none of these cases was the cause of death confirmed to be directly related to Renagel. All of these deaths occurred in either 2000 or 2001; no deaths associated with intestinal obstruction or intestinal perforation outside of Japan have occurred since 2001.

A total of 13 deaths in patients with ileus, intestinal obstruction or intestinal perforation on sevelamer hydrochloride have been reported in Japan since the 2003 product introduction: 6 in 2003, 4 in 2004, and 3 in 2005. Genzyme's comprehensive review of these reports revealed several confounding factors including: underlying co-morbid conditions, prior history of abdominal surgery, multiple concomitant medications and herbal or other traditional remedies, administration of enemas, which might have contributed, or did contribute, to the event of perforation when it occurred, and other causes of death, including cardiac events. In all cases, the cause of death was not confirmed to be directly related to sevelamer hydrochloride.

Genzyme has evaluated the events of ileus, gastrointestinal obstruction and gastrointestinal perforation and reviewed the occurrence of these events against other sources including the USRDS Database, which is composed of information on patients with end-stage renal disease. Between 1998 and 2003, the USRDS Database¹⁰ notes a declining percentage of total hospital discharge codes (DRGs) for gastrointestinal obstruction and from 1996 to 2003, the death rate from bowel perforation (0.6 per 1000 patient years at risk) has remained constant. It is important to note that, during the period from 1998 to 2003, the utilization of Renagel continued to increase annually.

Genzyme's comprehensive review of the post-marketing reports of ileus, gastrointestinal obstruction or gastrointestinal perforation revealed that complex co-morbidities and concomitant medications often contributed to the event. Furthermore, adverse events reported for patients in the United States, Europe, Brazil, Canada and Israel on Renagel were consistent with patients' underlying renal disease and hemodialysis status. Thus, as a result of its review of both the AERS and other data sources, Genzyme has found no evidence of a safety risk of ileus, gastrointestinal obstruction or gastrointestinal perforation to the population with regard to the use of Renagel.

III. Safe and effective dosing for Renagel is widely known and understood.

The Citizen Petition inaccurately suggests that reports of GI adverse events are correlated with increased dosing of Renagel to meet the more stringent K/DOQI guidelines which were issued in 2003. In fact, 88 percent of the reports of ileus, gastrointestinal obstruction and gastrointestinal perforation received since the introduction of Renagel in 1999 were reported from Japan, correspond

¹⁰ See Attachment 4.

to the Japanese launch of sevelamer hydrochloride in June 2003, and are unrelated to dosing modifications that may have resulted from revised 2003 K/DOQI guidelines. Genzyme data establish that dosing levels for Renagel have remained largely constant, at levels well below those stated in the Citizen Petition.

IV. The AERS database numbers of intestinal obstructions and perforations do not support modifications of the labeling for Renagel tablets.

The Citizen Petition requests that, should FDA decline to withdraw market approval, the labeling for Renagel be revised to warn physicians about occurrences of intestinal obstruction and perforation, including the use of a black box warning. The AERS database numbers do not support such an action.

In its very recent letter to Congressman Souder, described above, FDA explains comprehensively why it does not believe the AERS data provide a sufficient basis for either FDA or sponsor action, as they do not support causality assessments or allow for accurate assessment of the frequency of an event in relation to drug use. As Genzyme has demonstrated, the numbers of adverse events presented by Dr. Nolan's interpretation of the AERS database show substantial duplication, and thus significantly exceed those in the Genzyme Global Safety data base, as reported to FDA.

Further, the reports found in the AERS database have been clearly identified as originating almost completely from one geographic location, Japan, and, documented duplicative reporting aside, can be attributed to multiple factors including: varied ethnic and cultural factors, diet differences, differences in medicinal and healthcare practices, and proactive event reporting. In contrast, few similar events have been reported in the more than 50 other countries where the drug is marketed, including the United States, where usage far exceeds that in Japan. Moreover, since originally identified, the number of reports in Japan has continued to decline. Finally, we note that in its present label, Renagel is already contraindicated in patients with bowel obstruction and cautions the use of Renagel in patients with severe gastrointestinal motility disorders or major gastrointestinal surgery. Accordingly, we believe no action with respect to the labeling for Renagel is warranted as a result of the AERS data.

Moreover, while the petitioner refers to certain other phosphate binders (PhosLo^{®11} and Fosrenol^{®12}) as alternative, "at-least-as-effective," therapies which are "FDA-approved and marketed

¹¹ Dr. Nolan states in the Citizen Petition that he has served as a consultant for Nabi Biopharmaceuticals, the manufacturer of PhosLo, one of the products which he compares favorably to Renagel. In light of this consulting arrangement, which may be ongoing, we find the statement that he was "not compensated for submitting the petition" insufficient to disclose potential conflict-of-interest. We would suggest, therefore, that Dr. Nolan supplement the record with a more detailed description of his past and present consulting arrangement with Nabi, which should also include whether and to what extent he received any direct or indirect assistance from Nabi in the preparation of the Citizen Petition.

¹² Fosrenol (lanthanum hydrochloride), marketed by Shire, was first commercially marketed in 2004, and we submit that its post marketing safety profile has yet to be fully established.

in the United States,” and “which have not been reported to cause gastrointestinal perforations,” Genzyme submits that there is strong, positive clinical evidence of the safety of Renagel compared to calcium-based phosphate binders that contradicts the limited value of the AERS data. First, as documented at length above, the positive safety profile of Renagel is well established. Taking into account global Renagel patient exposure, reported adverse events are few and are generally consistent with patients’ underlying disease. Reports of ileus, gastrointestinal obstruction and gastrointestinal perforation are extremely rare when global adverse event data, absent Japan during the period 2003-2005, is taken as a whole, and particularly in the United States, where reports of these events are virtually nonexistent, despite widespread use. In addition, several well-controlled clinical studies comparing sevelamer and calcium phosphate binder use have demonstrated that, in the end stage renal disease patient population on dialysis, particularly in the majority of patients with preexisting calcification, progression of arterial calcification is observed. In contrast, patients on Renagel in these studies have consistently not shown similar progression.

In both Chertow, G.M., *et al.* (2005) *Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients*,¹³ and Asmus, H.G., *et al.*, (2005) *Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density*,¹⁴ calcium-based phosphate binder use in hemodialysis patients was shown to be associated with progressive arterial calcification. More recently, in Block, G.A., *et al.* (2005) *Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis*,¹⁵ while new hemodialysis patients with no evidence of coronary calcification showed little evidence of disease development over 18 months independent of phosphate binder therapy, subjects with evidence of at least mild coronary calcification at baseline had significant progression, with calcium-containing phosphate binder use resulting in more rapid progression of coronary calcification than sevelamer hydrochloride.

V. Conclusion

Genzyme respectfully submits that the available data demonstrate that the Citizen Petition is without merit. Its sole reliance on AERS data on Renagel cannot support either of the actions requested. The AERS data, as stated by FDA itself, are simply not sufficient to support regulatory action of this type. In the present case, the duplicative reporting of adverse events in the AERS database has been documented. Moreover, the frequency of events has been shown to derive mostly from a single country, something not disclosed in the petition. In that country, the available evidence suggests that reported events are attributable to cultural and other factors. Finally, the positive safety profile of Renagel is well established, while substantial clinical evidence attests to the relative safety and effectiveness of Renagel compared to calcium based phosphate binders in the health of patients with chronic kidney disease on hemodialysis.

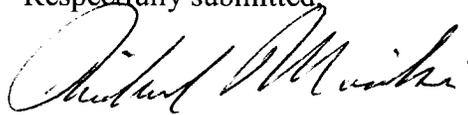
¹³ *Kidney International*, Vol. 68: 1815-1824.

¹⁴ *Nephrology Dialysis Transplantation*, Vol. 20: 1653-1661.

¹⁵ Block, G.A., *et al.* (2005) Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney International*, Vol. 68: 1815-1824. See Attachment 5.

For these reasons, the petition should be denied.

Respectfully submitted,



Richard A. Moscicki, M.D.
Chief Medical Officer
Senior Vice President – Biomedical and Regulatory
Affairs

Attachments